FIG. 1

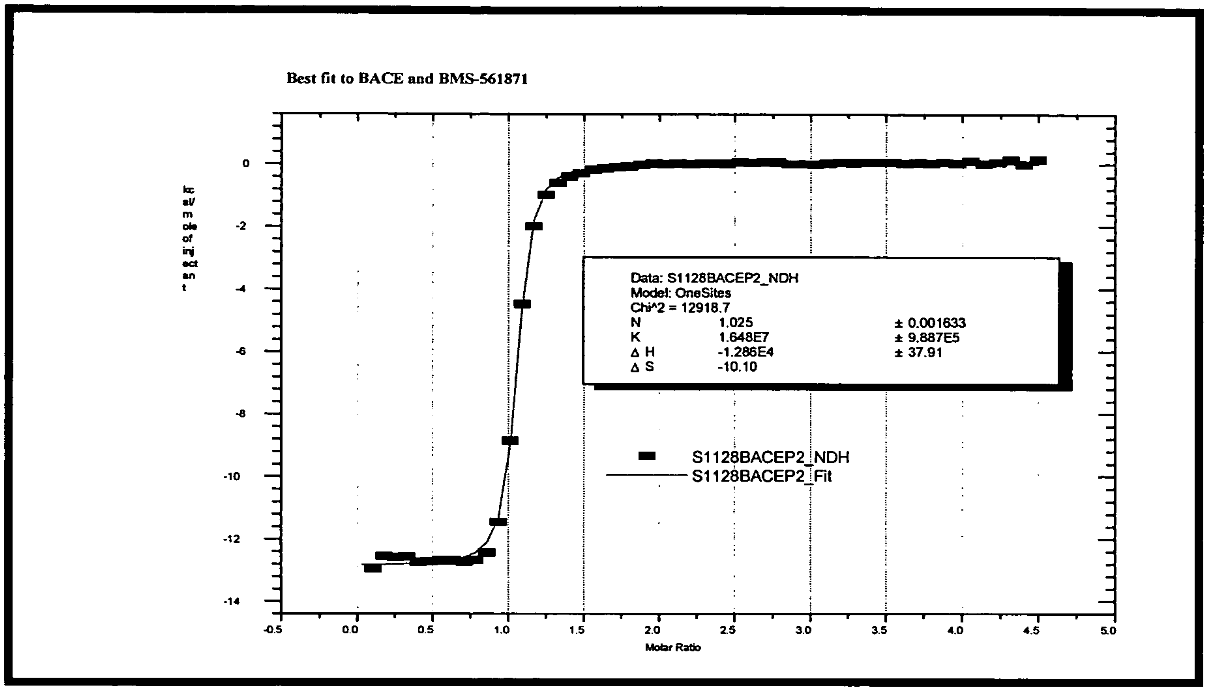

Best fit to BACE and BMS-561871
kcal/mole of injectant
0
-2
-4
-6
-8
-10
-12
-14
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
Molar Ratio
Data: S1128BACEP2_NDH
Model: OneSites
Chi^2 = 12918.7
N 1.025 ± 0.001633
K 1.648E7 ± 9.887E5
Δ H -1.286E4 ± 37.91
Δ S -10.10
S1128BACEP2_NDH
S1128BACEP2_Fit

FIG. 2

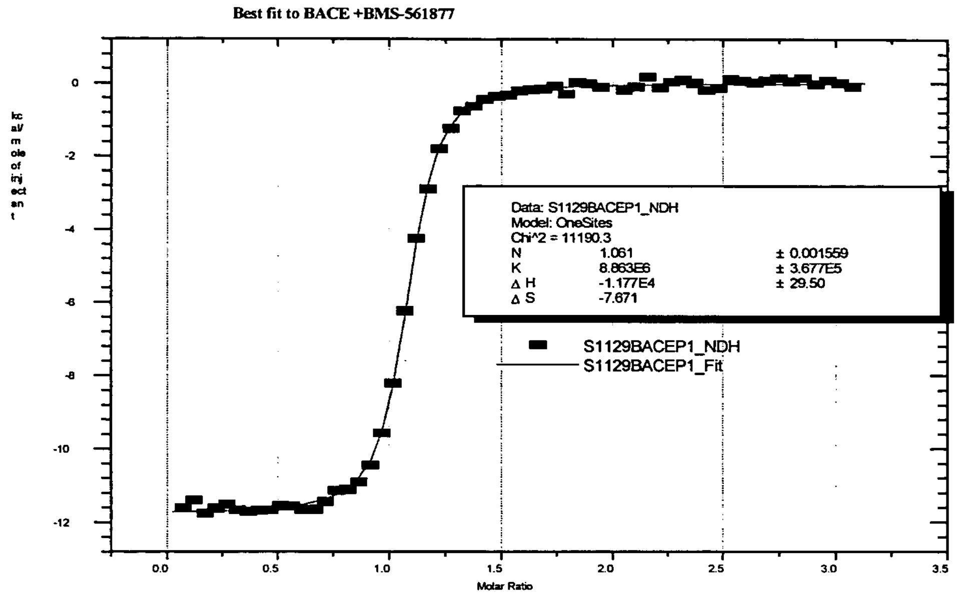

Best fit to BACE +BMS-561877
kcal/mole of injectant
0
-2
-4
-6
-8
-10
-12
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
Molar Ratio
Data: S1129BACEP1_NDH
Model: OneSites
Chi^2 = 11190.3
N 1.061 ± 0.001559
K 8.863E6 ± 3.677E5
Δ H -1.177E4 ± 29.50
Δ S -7.671
S1129BACEP1_NDH
S1129BACEP1_Fit

FIG. 3

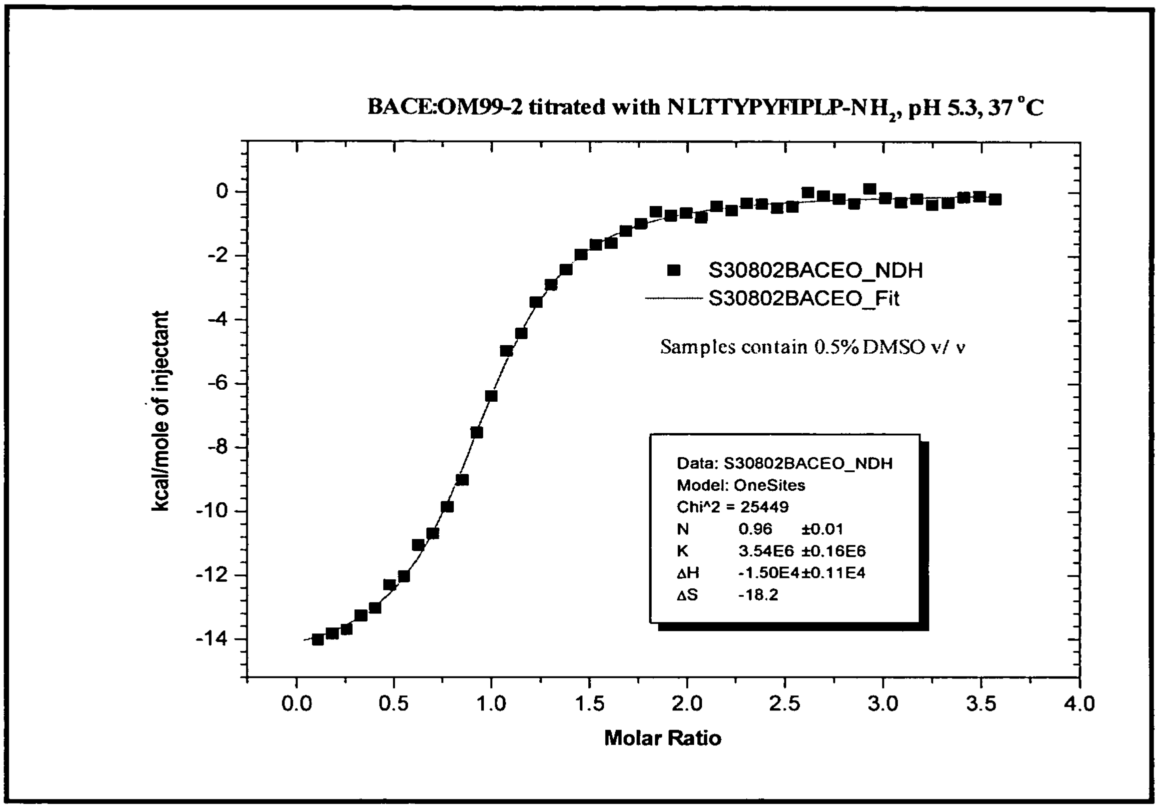
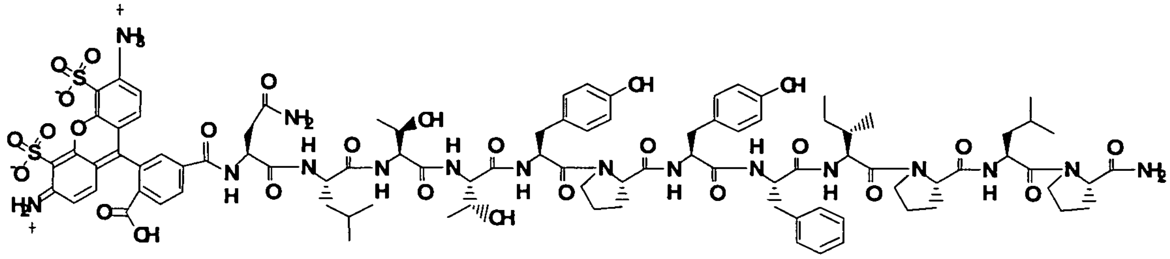
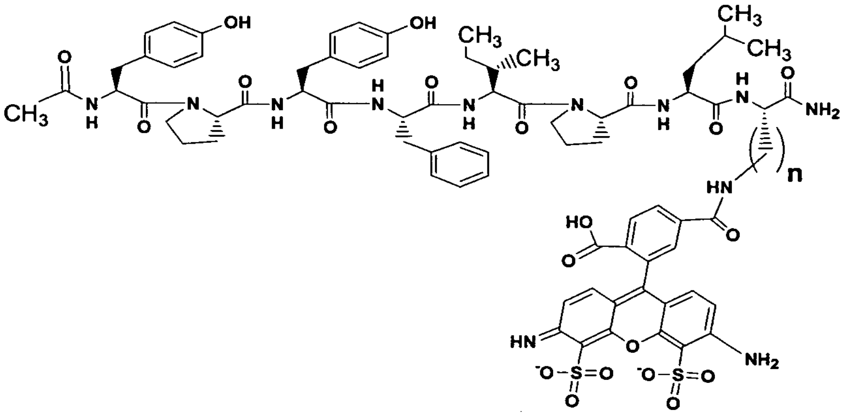

BACE:OM99-2 titrated with NLTTYPYFIPLP-NH$_2$, pH 5.3, 37 °C
kcal/mole of injectant
0
-2
-4
-6
-8
-10
-12
-14
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Molar Ratio
■ S30802BACEO_NDH
S30802BACEO_Fit
Samples contain 0.5% DMSO v/ v
Data: S30802BACEO_NDH
Model: OneSites
Chi^2 = 25449
N 0.96 ±0.01
K 3.54E6 ±0.16E6
ΔH -1.50E4±0.11E4
ΔS -18.2

FIG. 4

Molecule X



Molecule Yn (n=1-4)



Molecule Z

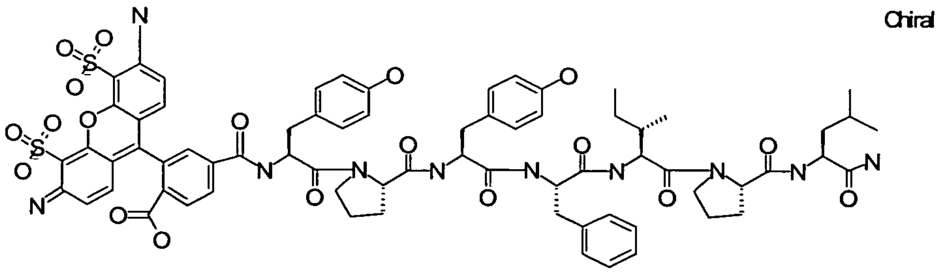


FIG. 5

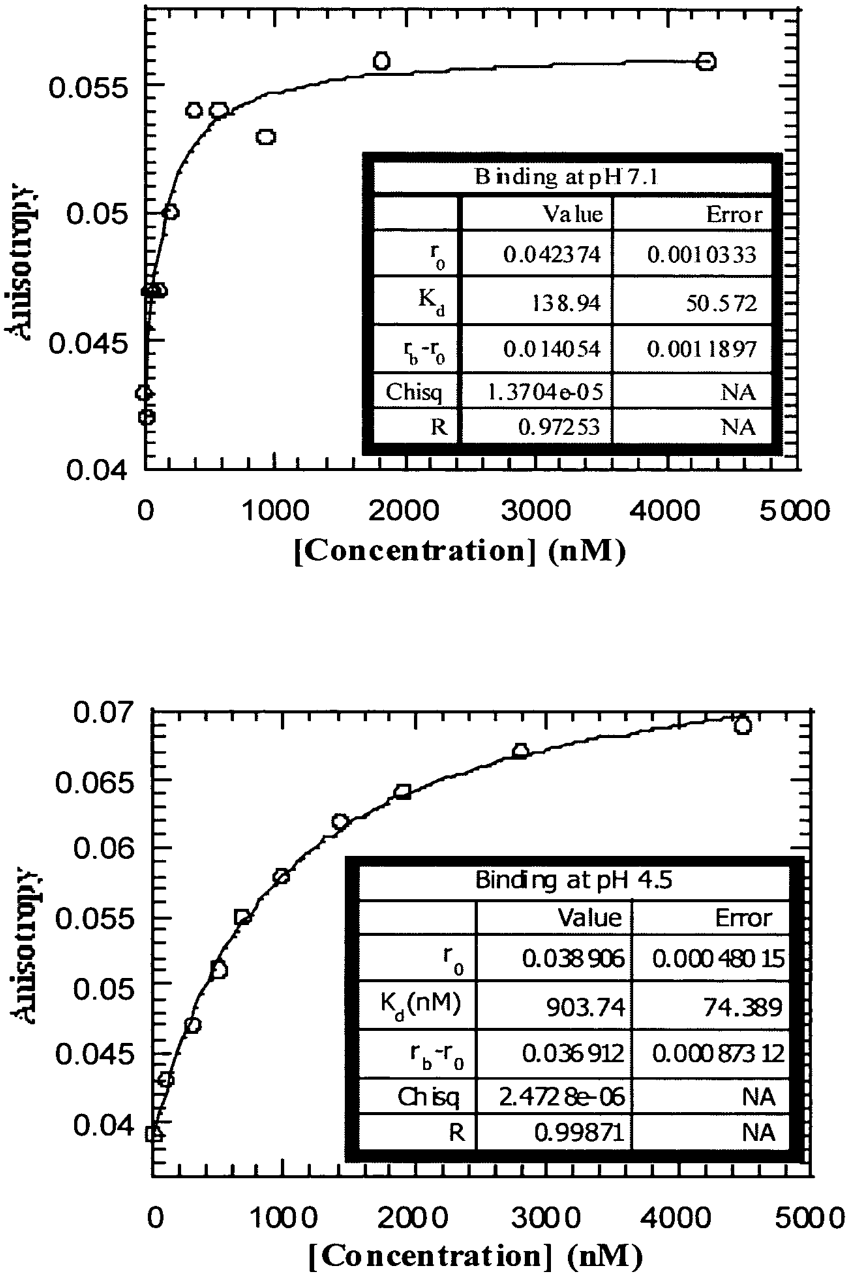

0.055
0.05
0.045
0.04
Anisotropy
0
1000
2000
3000
4000
5000
[Concentration] (nM)
Binding at pH 7.1
Value
Error
r_0 0.042374 0.0010333
K_d 138.94 50.572
r_b-r_0 0.014054 0.0011897
Chisq 1.3704e-05 NA
R 0.97253 NA
0.07
0.065
0.06
0.055
0.05
0.045
0.04
Anisotropy
0
1000
2000
3000
4000
5000
[Concentration] (nM)
Binding at pH 4.5
Value
Error
r_0 0.038906 0.00048015
K_d(nM) 903.74 74.389
r_b-r_0 0.036912 0.00087312
Chisq 2.4728e-06 NA
R 0.99871 NA

FIG. 6

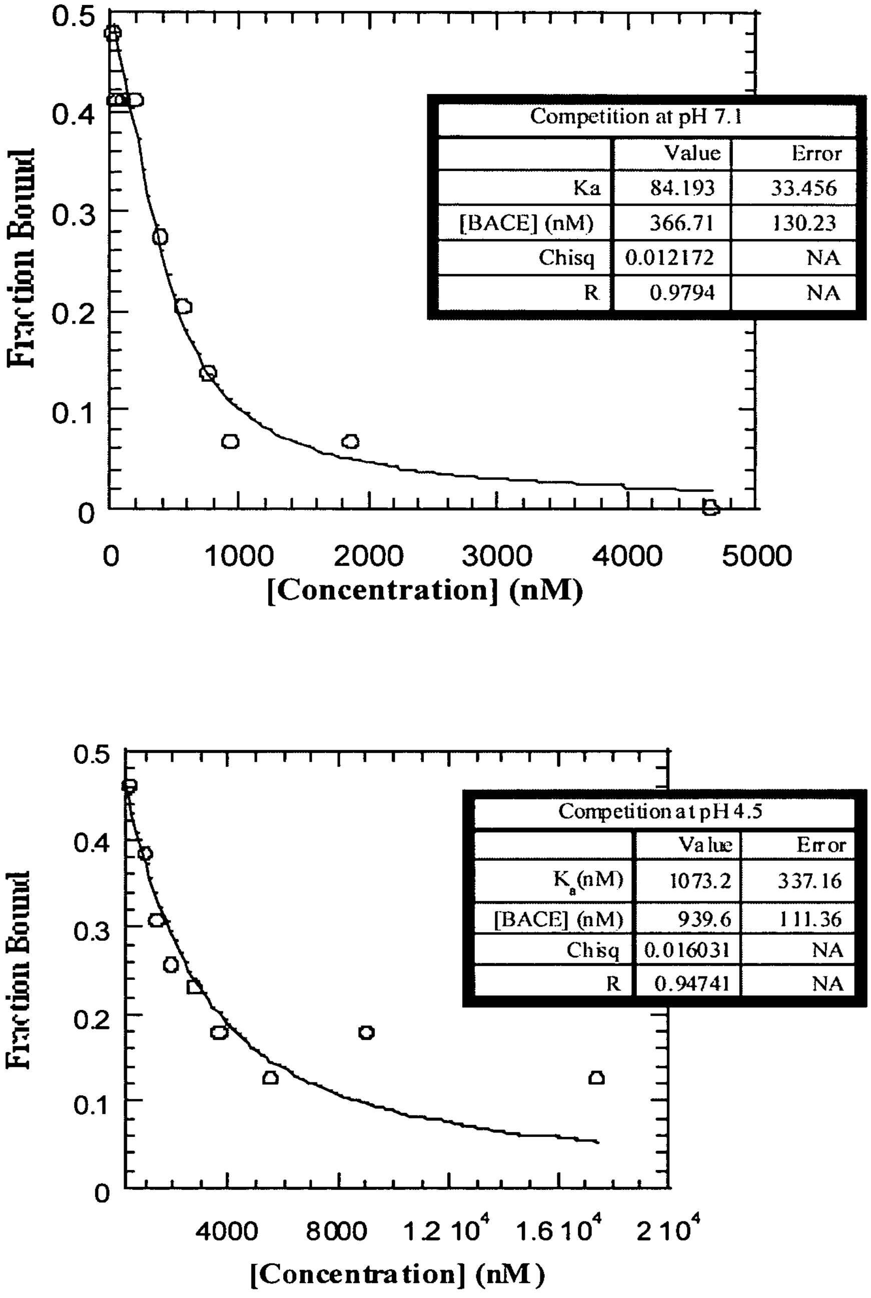

Competition at pH 7.1
Value
Error
Ka 84.193 33.456
[BACE] (nM) 366.71 130.23
Chisq 0.012172 NA
R 0.9794 NA
Fraction Bound
0.5
0.4
0.3
0.2
0.1
0
0
1000
2000
3000
4000
5000
[Concentration] (nM)
Competition at pH 4.5
Value
Error
K_a(nM) 1073.2 337.16
[BACE] (nM) 939.6 111.36
Chisq 0.016031 NA
R 0.94741 NA
Fraction Bound
0.5
0.4
0.3
0.2
0.1
0
4000
8000
$1.2\ 10^4$
$1.6\ 10^4$
$2\ 10^4$
[Concentration] (nM)

FIG. 7

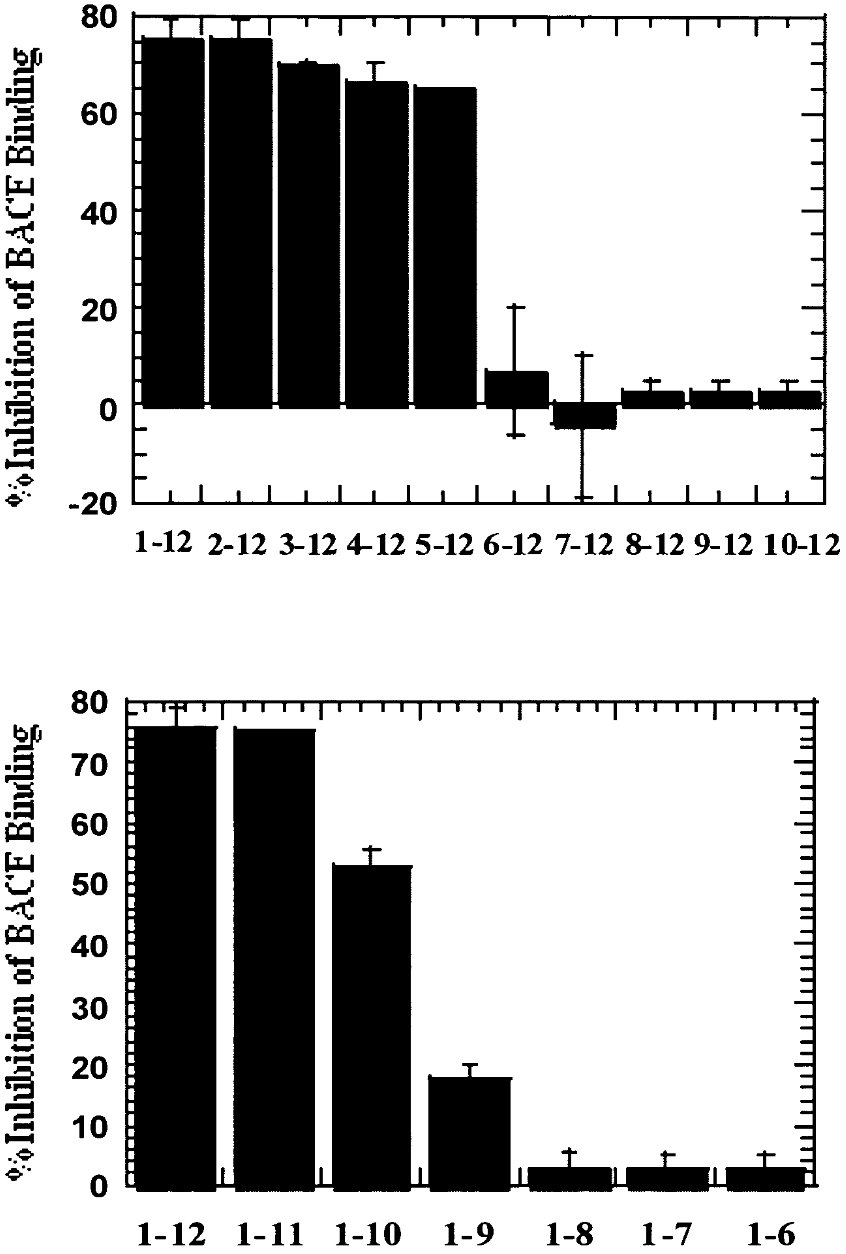
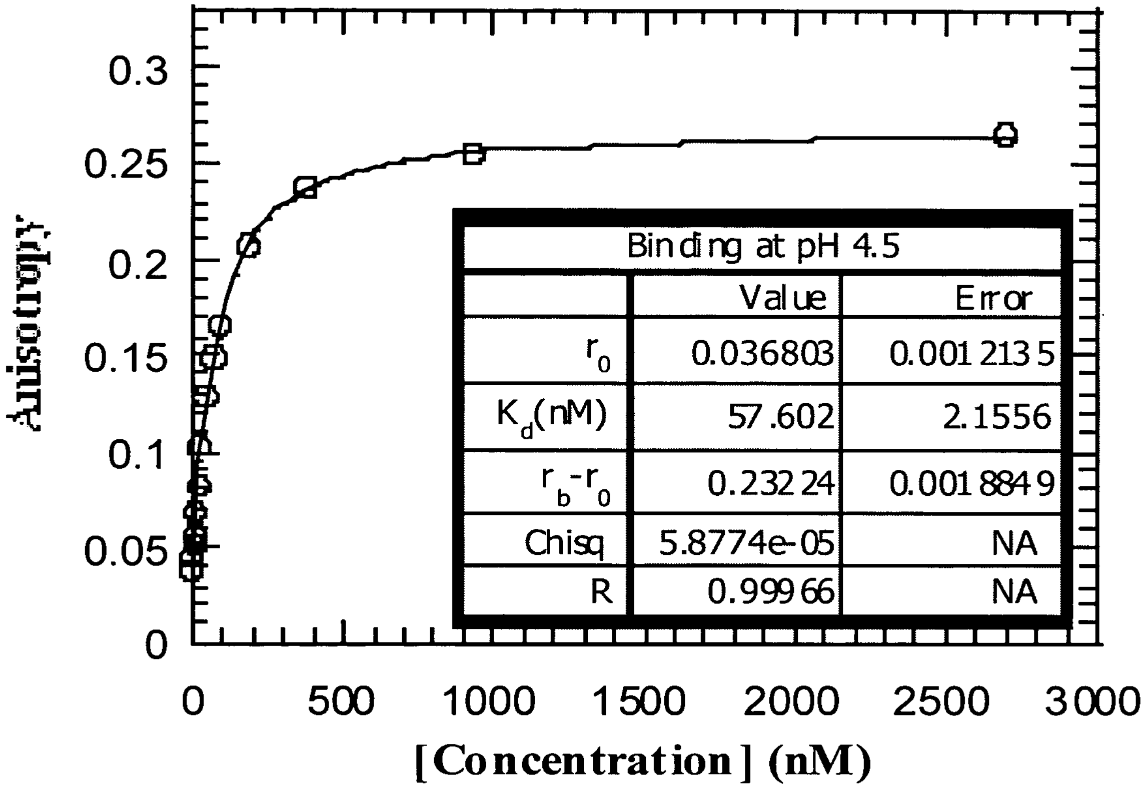
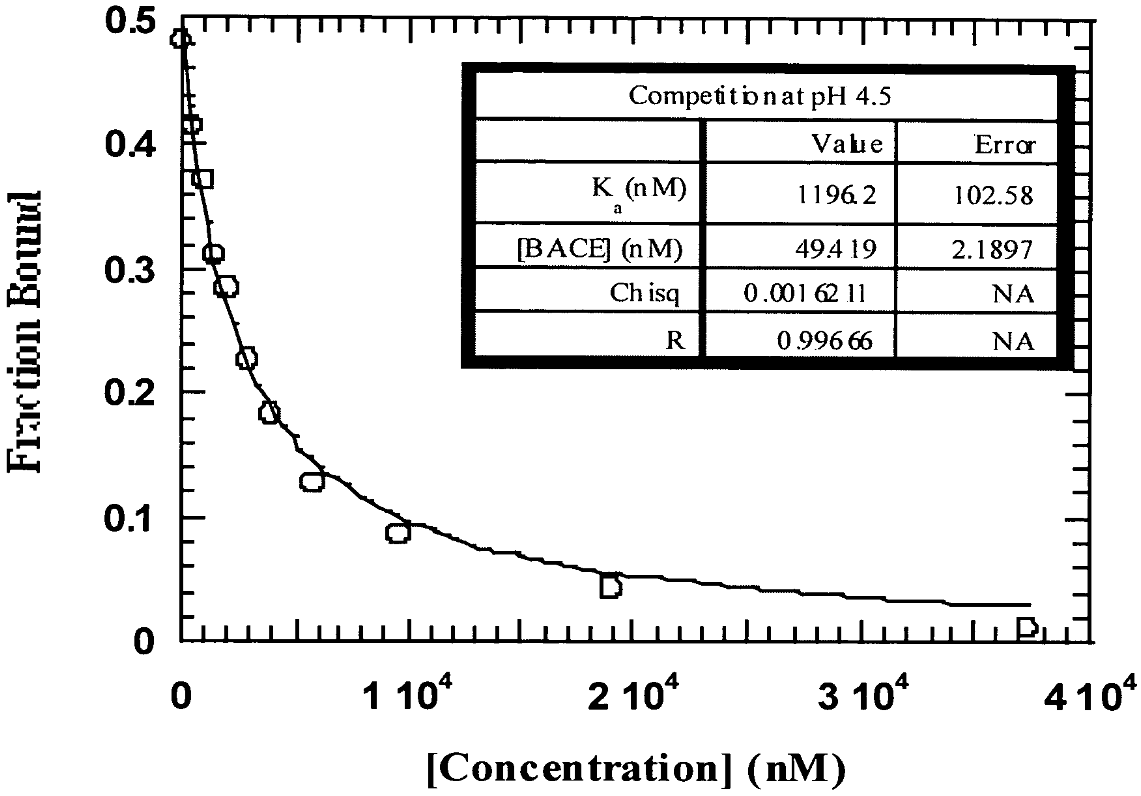

% Inhibition of BACE Binding
80
60
40
20
0
-20
1-12
2-12
3-12
4-12
5-12
6-12
7-12
8-12
9-12
10-12
% Inhibition of BACE Binding
80
70
60
50
40
30
20
10
0
1-12
1-11
1-10
1-9
1-8
1-7
1-6

FIG. 8



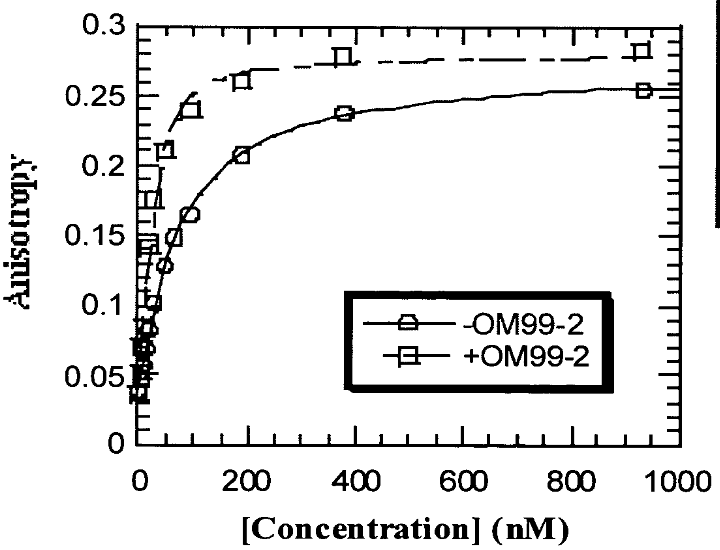
Binding at pH 4.5		
	Value	Error
r_0	0.036803	0.0012135
K_d(nM)	57.602	2.1556
r_b-r_0	0.23224	0.0018849
Chisq	5.8774e-05	NA
R	0.99966	NA

FIG. 9



Competition at pH 4.5		
	Value	Error
K_a (nM)	1196.2	102.58
[BACE] (nM)	49.419	2.1897
Chisq	0.0016211	NA
R	0.99666	NA

FIG. 10



Binding, -OM99-2		
	Value	Error
r_0	0.036803	0.0012135
K_d(nM)	57.602	2.1556
r_b-r_0	0.23224	0.0018849
Chisq	5.8774e-05	NA
R	0.99966	NA

Binding, +OM99-2		
	Value	Error
r0	0.03627	0.0038829
Kd	9.5896	1.5032
r_b-r_0	0.24396	0.0054788
Chisq	0.00033572	NA
R	0.9981	NA

FIG. 11

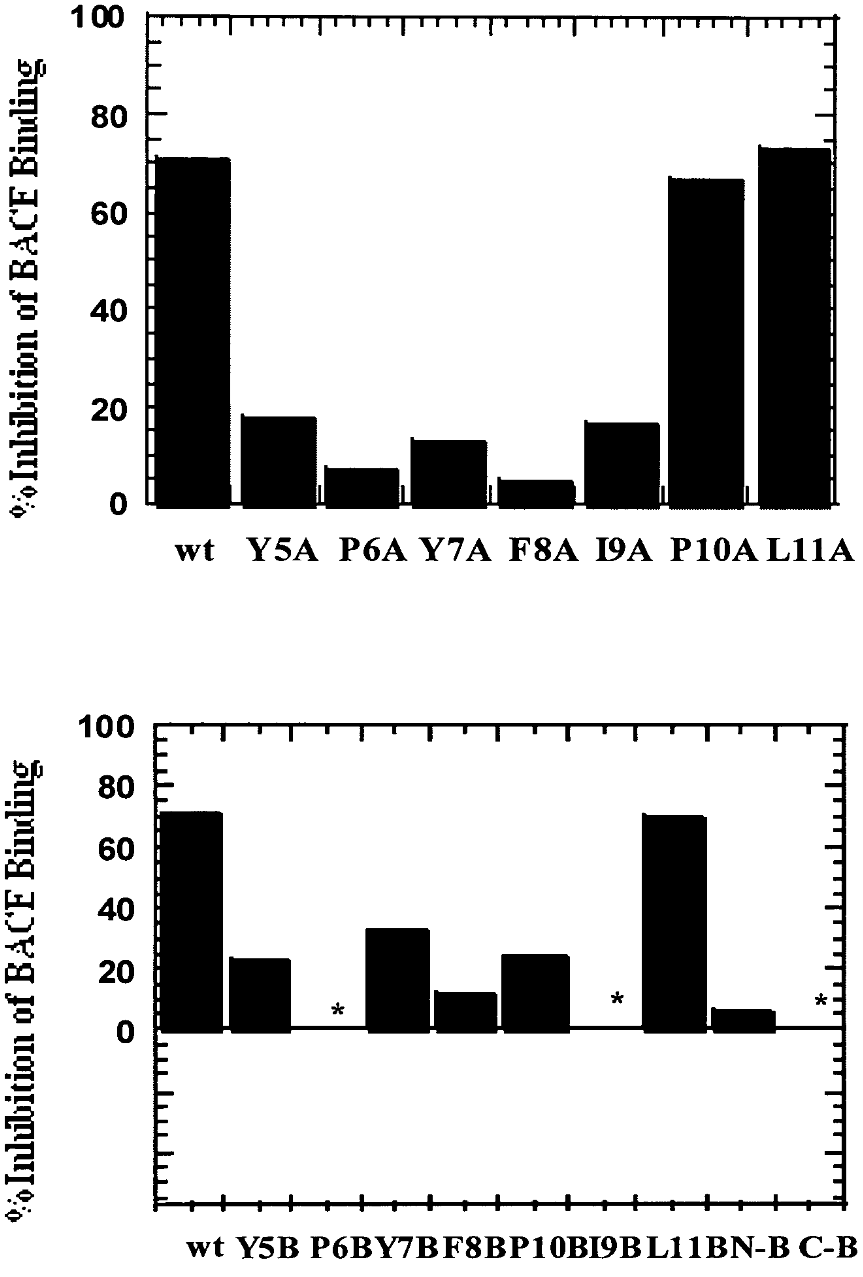

% Inhibition of BACE Binding
100
80
60
40
20
0
wt
Y5A
P6A
Y7A
F8A
I9A
P10A
L11A
% Inhibition of BACE Binding
100
80
60
40
20
0
*
*
*
wt
Y5B
P6B
Y7B
F8B
P10B
I9B
L11B
N-B
C-B

FIG. 12

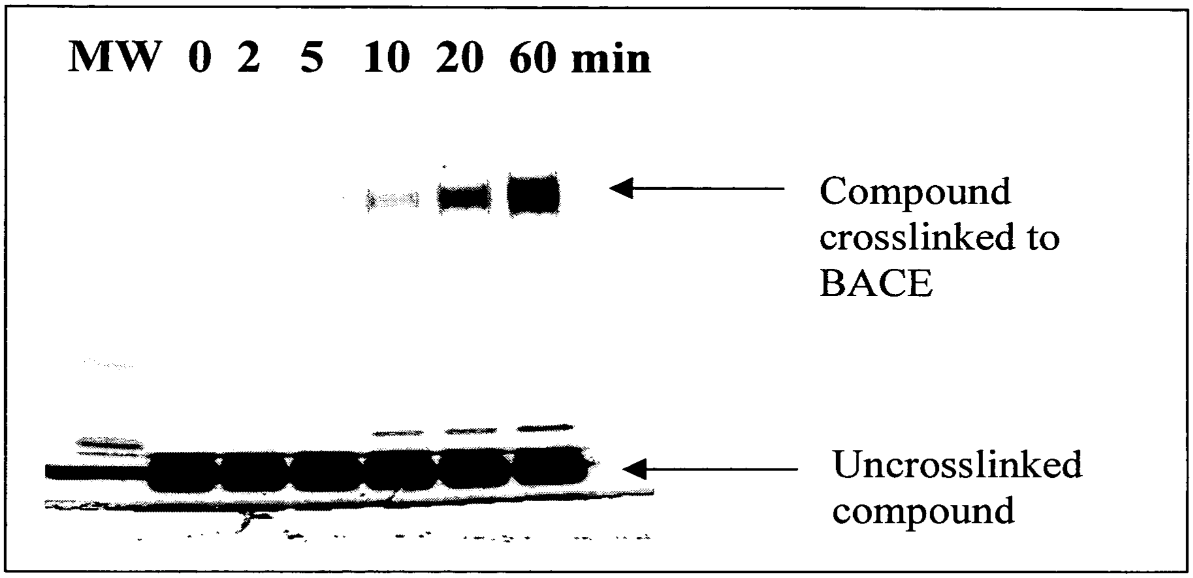
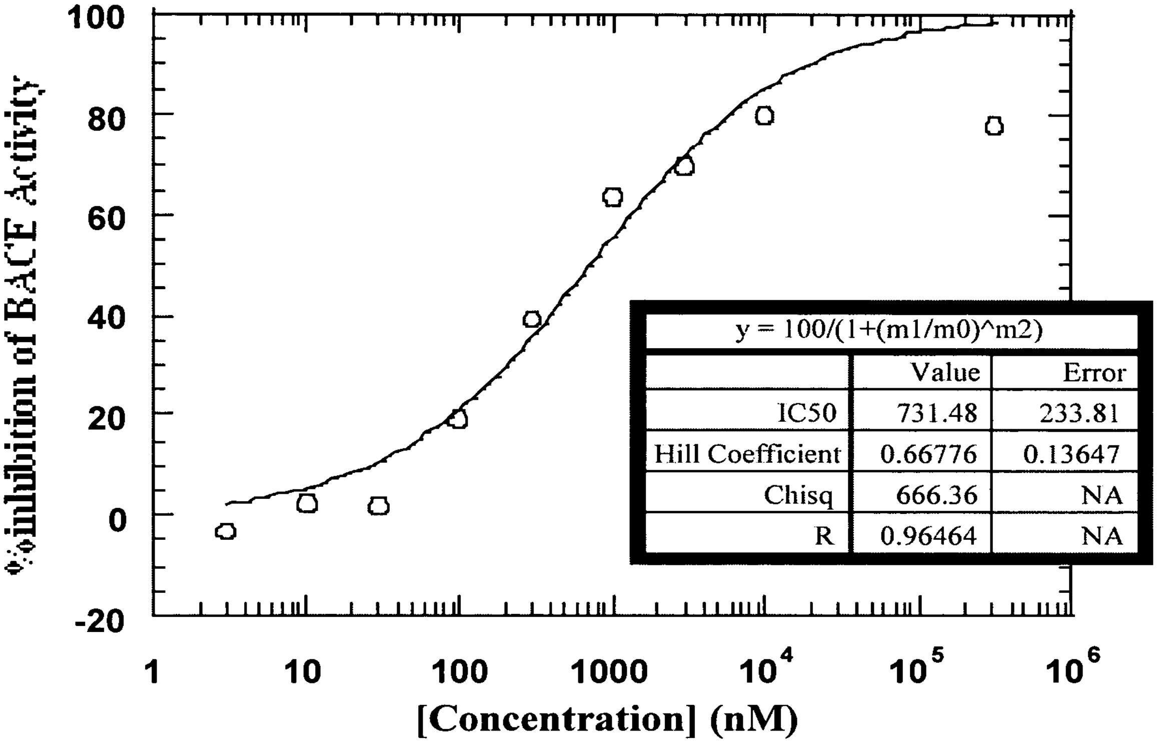

MW 0 2 5 10 20 60 min
Compound crosslinked to BACE
Uncrosslinked compound

FIG. 13



y = 100/(1+(m1/m0)^m2)		
	Value	Error
IC50	731.48	233.81
Hill Coefficient	0.66776	0.13647
Chisq	666.36	NA
R	0.96464	NA

FIG. 14

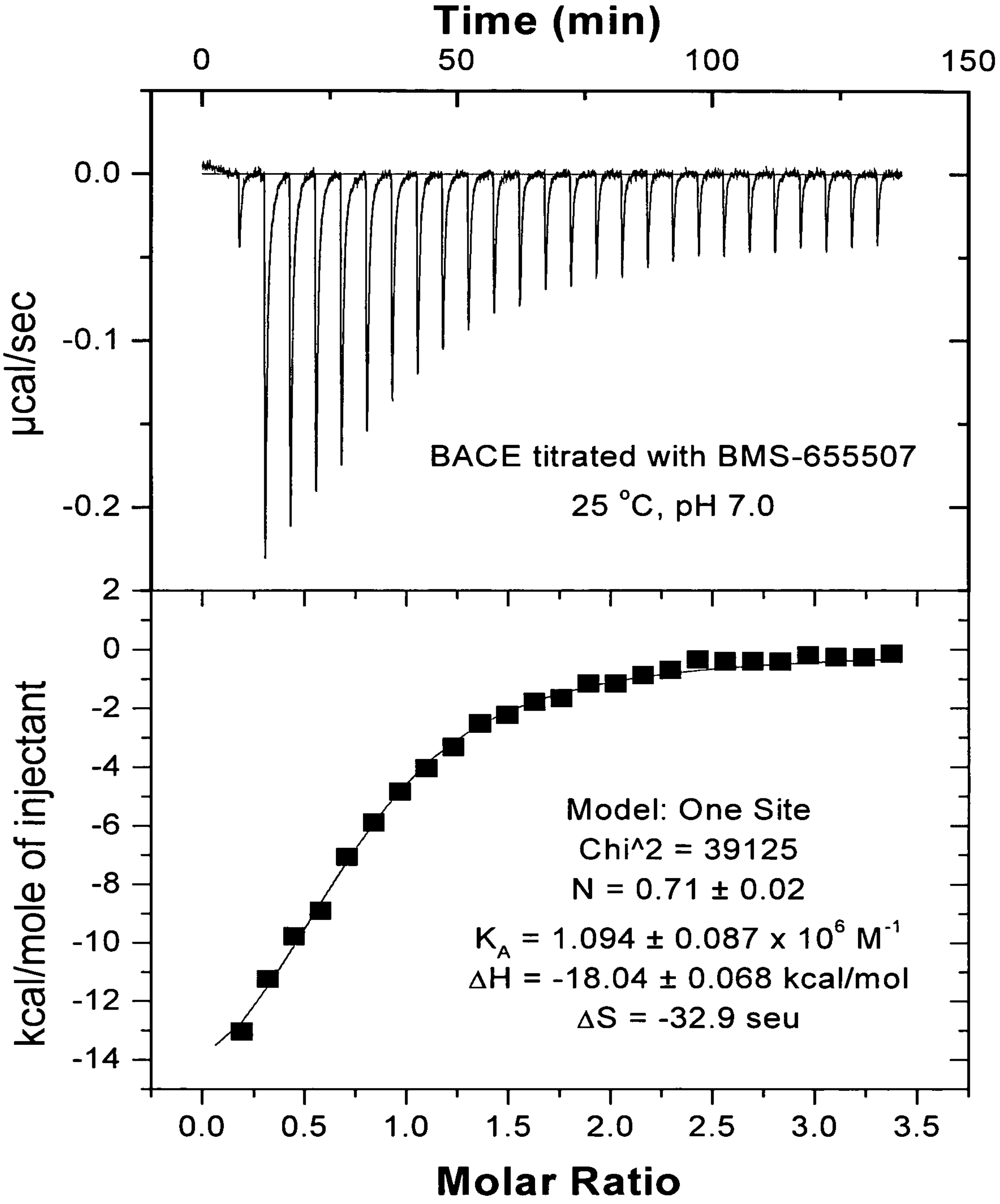
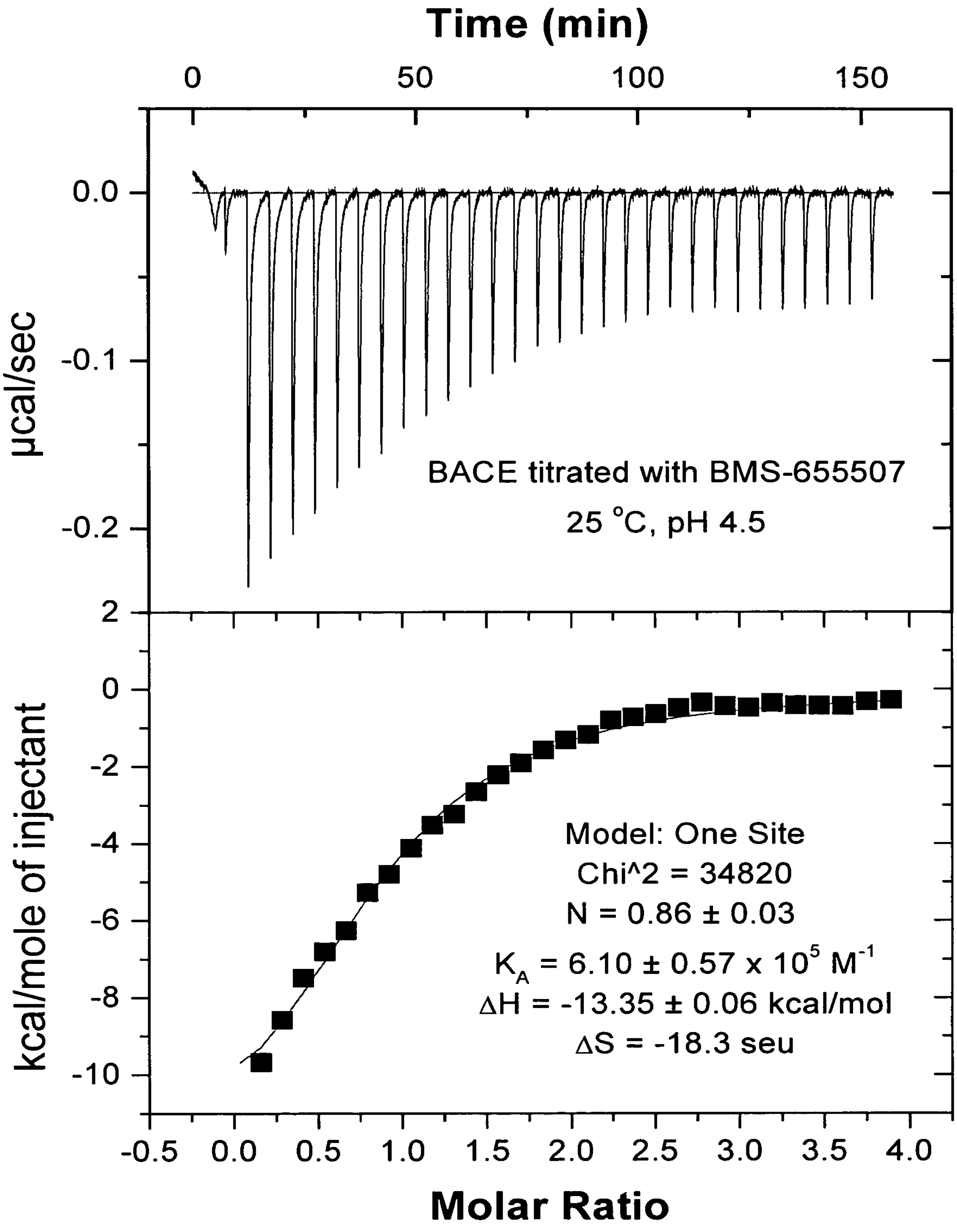

Time (min)
0
50
100
150
µcal/sec
0.0
-0.1
-0.2
BACE titrated with BMS-655507
25 °C, pH 7.0
kcal/mole of injectant
2
0
-2
-4
-6
-8
-10
-12
-14
Model: One Site
Chi^2 = 39125
N = 0.71 ± 0.02
K_A = 1.094 ± 0.087 x 10^6 M^-1
ΔH = -18.04 ± 0.068 kcal/mol
ΔS = -32.9 seu
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
Molar Ratio

FIG. 15


Time (min)
0
50
100
150
µcal/sec
0.0
-0.1
-0.2
2
0
-2
-4
-6
-8
-10
BACE titrated with BMS-655507
25 °C, pH 4.5
kcal/mole of injectant
Model: One Site
Chi^2 = 34820
N = 0.86 ± 0.03
K_A = 6.10 ± 0.57 x 10^5 M^-1
ΔH = -13.35 ± 0.06 kcal/mol
ΔS = -18.3 seu
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Molar Ratio